Remarks

This amendment is made to conform the application with the provisions of 37 CFR §§1.821 through 1.825 and to correct inadvertent typographical errors throughout the specification. I hereby certify that no new material is being added by this submission.

The Commissioner is hereby authorized to charge any fees under 37 CFR 1.16 or 1.17 as required by this paper to Deposit Account No. 19-0065.

Respectfully submitted,

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DRP/sl
Attachment: New pages 1-6 (Sequence Listing) of the subject specification; Marked-Up Version of Substituted Paragraphs.

Marked-Up Version of Substituted Paragraphs

Paragraph on page 6, beginning at line 25:

Preferably the amino acid tail comprises HHHHHHGS (SEQ ID NO. 2).

Paragraph on page 7, beginning at line 28:

Figure 1 shows the structure and sequence of the antennapedia homeodomain (SEQ ID NO. 6) obtainable from *Drosophila*; and

Paragraph on page 8, beginning at line 1:

Figure 2 further shows two mutants, designated pAntp [50H] 50A (SEQ ID NO. 7) and pAntp 40P2 (SEQ ID NO. 8).

Paragraph on page 10, beginning at line 4:

WO97/12912 also to CNRS discloses the actual sequence of the helix 3 of pAntp, and variants thereof. These also are incorporated herein by reference. In particular, the 3 helix is said to have the sequence:

Arg-Gln-Ile-Lys-Ile-Trp-Phe-Gln-Asn-Arg-Arg-Met-Lys-Trp-Lys-Lys (SEQ ID NO. 3)

The variants are said to have the sequence:

X1-X2-X3-X4-X5-X6-X7-X8-X9-X10-X11-X12-X13-X14-X15-X16 (SEQ ID NO. 4)

or

X16-X15-X14-X13-X12-X11-X10-X9-X8-X7-X6-X5-X4-X3-X2-X1 (SEQ ID NO. 5)

wherein each X represents an α-amino acid, with X6 representing [trytophane] tryptophan; said peptide comprising between 6 and 10 hydrophobic amino acids.

Paragraph on page 10, beginning at line 15:

Other variants are [desclosed] disclosed in for example, Gehring W (1987) Homeo Boxes in the Study of Development. *Science* **236** 1245-1252 discloses a homeodomain of 62 amino acids, i.e. with glu at position 0 and lys at position 61. Bloch-Gallego E [*at al*] *et al.* (1993) Antennapedia Homeobox Peptide Enhances Growth and Branching of Embryonic Chicken Motoneurons In Vitro.

The Journal of Cell Biology **120**(2) 485-492 discloses a mutant called [pAntp40P2] pAntp 40P2 (SEQ ID NO. 8) that was still able to translocate through the motoneuron membrane and to reach the nucleus. In this mutant the leucine and threonine residues in positions 40 and 41 were replaced by two proline residues. Le Roux *et al.* (1993). Neurotropic activity of the Antennapedia homeodomain depends on its specific DNA-binding properties. *Proc. Natl. Acad. Sci.* **90** 9120-9124 discloses two mutants pAntp 50A (SEQ ID NO. 7) and pAntp 40P2 (SEQ ID NO. 8) as shown in Figure 2 which retain the ability to translocate through the neuronal membrane. Schutze-Redelmeier M-P *et al.* (1996) *supra* disclose that a 16 amino acid C-terminal (third helix) segment has been used to address oligonucleotides and oligopeptides to the cytoplasm and nuclei of cells in culture.

Paragraph on page 11, beginning at line 8:

Preferably, the first and second regions are linked by a cleavable linker region this may be any region suitable for this purpose. Preferably, the cleavable linker region is a protease cleavable linker, although other linkers, cleavable for example by small molecules, may be used. These include Met-X sites, cleavable by cyanogen bromide, Asn-Gly, cleavable by hydroxylamine, Asp-Pro, cleavable by weak acid and Trp-X [celavable] cleavable by, *inter alia*, NBS-skatole. Protease cleavage sites are preferred due to the milder cleavage conditions necessary and are found in, for example, factor Xa, thrombin and collagenase. Any of these may be used. The precise sequences are available in the art and the skilled person will have no difficulty in selecting a suitable cleavage site. By way of example, the protease cleavage region targeted by Factor Xa is I E G R (SEQ ID NO. 9). The protease cleavage region targeted by Enterokinase is D D D D K (SEQ ID NO. 10). The protease cleavage region targeted by Thrombin is L V P R G (SEQ ID NO. 11). Preferably the cleavable linker region is one which is [targetted] targeted by endocellular proteases.

Paragraph on page 12, beginning at line 23:

The nucleic acid binding domain may be an RNA binding domain, or preferentially, a DNA binding domain, e.g. the DNA [bidning] binding domain of a transcription factor, particularly a yeast or human transcription factor. Preferred is A GAL4 derivable domain, mediating the selective binding of the protein of the invention to the DNA sequence CGGAGGACAGTCCTCCG (SEQ ID

NO. 12) (Cavey *et al* J Mol Biol 209:423, 1989). Most preferably the DNA binding domain consists of GAL4 amino acids 2 to 147. A DNA binding domain may bind to single-stranded or to a double stranded DNA on the second domain.

Paragraph on page 27, beginning at line 25:

The monoclonal antibody (mAb) 4 D 11 was found by screening in ELISA [hydridomas] hybridomas generated from a mouse that was immunised with a recombinant protein containing a six histidine tail at its amino-terminal end. The antibody is available from Imperial College of Science, Technology and Medicine, Sherfield Building Exhbition Rd, London SW7 2AZ, UK c/o ic Innovations Ltd, 47 Princes Gate, London SW7 2AZ, UK. A molecular characterisation of the epitope showed that this mAb recognises the amino acid sequence HHHHHHGS (SEQ ID NO. 2) both at the amino and at the carboxyl terminal end of recombinant proteins. The antibody has an IgG1 isotype and can be easily purified on protein A column. Our results indicate that 4 D 11 recognises the recombinant proteins containing the HHHHHHGS (SEQ ID NO. 2) in ELISA immunoblot, immuno-fluorescence. In addition purified 4 D 11 coupled to beads (affi-gel or CNBR activated sepharose) can be used to purify recombinant proteins under native conditions.